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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 01/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/771,312	JAKOBOVITS ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12,14,15 and 39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12,14,15 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Response to the Amendment

The Amendment filed on 10/13/2005 in response to the previous Non-Final Office Action (05/04/2005) is acknowledged and has been entered.

12, 14-15 and 39 are currently pending and under consideration

The Declaration under 37 CFR 1.132 filed on 10/13/2005 by Karen Jane Meyrick Morrison is acknowledged and has been considered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Rejections Maintained:

Claims 12, 14-15 and 39 **remain** rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Claims 12, 14-15 and 39 are directed to an isolated recombinant protein comprising the amino acid sequence of SEQ ID NO: 2, wherein the recombinant protein is encoded by a nucleotide sequence of SEQ ID NO: 1. However, neither the specification nor any art of record teaches what the amino acid sequence of SEQ ID NO: 2 is, how it functions, or a specific and well-established utility as claimed. The specification asserts (page 15, lines 28-29 and page 16, lines 1-18) that the polypeptides of the invention can be utilized to generate antibodies for use in detecting 84P2A9 overexpression or the metastasis of prostate cells and/or cells of other cancers expressing the gene. Thus, it presumed that there is a correlation between the overexpression of the polypeptide and a particular disease state. Furthermore, the specification teaches (page 18, lines 15-17) that the proteins of the invention may also be used in the forensic analysis of tissues of unknown origin.

The instant situation is directly analogous to that which was addressed in *Brenner v. Manson,* 148 U.S.P.Q. 689 (1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anti-tumor activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. §101, which requires that an invention must have either an immediately apparent or fully disclosed "real world" utility. The court held that:

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. . . . [u]nless and until a process is refined and developed to this point-where *specific* benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field. . . . a patent is not a hunting license. . . .[i]t is not a reward for the search, but compensation for its successful conclusion.

Although the specification discloses a nexus between the polynucleotide expression and a disease state (see for example page 75, Example 3), the specification does not disclose a correlation between any specific disorder and an altered level or form of the claimed polypeptide. If a molecule such as the polypeptide of SEQ ID NO: 2 is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polypeptide to be used in a diagnostic manner. Many polypeptides may be expressed in normal tissues, as well as diseased tissues. Therefore, one needs to know, e.g., that the claimed polypeptide is present only in cancer tissue to the exclusion of normal tissue. Thus, in the absence of any correlation between the claimed polypeptide with any known disease or disorder, any information obtained from various expression profiles in both normal and diseased tissue only serves as the basis for further research on the observation itself.

Furthermore, those of skill in the art recognize that over expression of a particular nucleic acid specific for a tissue type, does not necessarily correlate nor predict equivalent levels of polypeptide expression. There are many steps in the pathway leading from DNA to protein, and all of them can, in principle, be regulated. For example, Alberts *et al.* (Molecular Biology of the Cell, 3rd

edition, 1994, page 465) illustrate post-transcriptional regulation of ferritin wherein the translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferin receptor polypeptide is translated. Lewin, B. also teaches (Genes VI, Oxford University Press, Inc., NY, Chapter 29, 1997) that a major control point for genes exists during the initiation of transcription by the interaction of the RNA polymerase with its promoter. Concurring with Alberts *et al.*, Lewin further acknowledges downstream control of gene expression since translation of mRNA in the cytoplasm is also a point of control. Also, with regards to tumor associated antigens, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Furthermore, Mallampalli *et al.* (Biochem. J. Vol. 318, 1996, pages 333-341) teach that the glucocorticoid, betamethasone, increased mRNA expression of cholinephosphate cytidylyltransferase (CT) as determined by RT-PCR and Southern analysis, but did not alter the levels of the CT enzyme as assayed by Western blotting (abstract, and page 339, 2nd column, 2nd paragraph). Finally, Lewin acknowledges that control of gene expression can occur at multiple stages and that production of RNA *cannot inevitably* be equated with production of protein. Thus, the predictability of protein translation and its possible utility as a diagnostic are not necessarily contingent on the levels of mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. Therefore, absent evidence of the polypeptide expression including the correlation to a diseased state, one of skill in the art would not be able to predictably use the invention in a way that constitutes a specific and substantial utility and as disclosed do not meet the requirements of 35 U.S.C. §101 as being useful.

Claims 12, 14-15 and 39 also **remain** rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

In response to the rejection, Applicants assert that they are not asserting a broad or general utility, but instead, are asserting that this protein can be used as a therapeutic target to treat cancerous prostate cells. For example, Applicants contend that the protein is useful to target a therapeutic compound, such as an antibody which specifically binds to the protein, to cancerous

prostate cells. As such, Applicants submit that the claimed protein is useful as a therapeutic target to treat prostate cancer is a specific utility. Applicants further argue that the present application contains evidence that the novel gene, which encodes the target protein, expresses mRNA in normal and cancerous prostate cancer cells (Specification, page 75, line 13 to page 76, line 8, see also Figures 4 and 5). Thus, Applicants contend that this data is sufficient to support Applicants asserted utility because one of ordinary skill in the art would have a reasonable belief that protein would be expressed by the mRNA transcripts detected in the target cells. Moreover, Applicants assert that based on 84P2A9 gene expression in prostate cancer, the 84P2Ap proteins encoded by and translated from the detected mRNA detected in the target cells have substantial utility as prostate cancer therapeutic target. Furthermore, Applicants submit that the asserted utility is practical, based on a well-recognized need in the art for additional prostate cancer markers, particularly those which show selective expression on prostate cancer cells over normal prostate cancer cells. Additionally, Applicants attempt to discredit the publication supporting the assertion that one of ordinary skill in the relevant art would reasonably doubt that protein is produced from a cancer cell in which mRNA for that protein has been detected. In short, Applicants contend the following: Alberts et al. neither teaches nor suggest that absolutely no transferring or ferritin are produced; Lewis, B is taken out of context because it is clear that the cytoplasmic regulation of eukaryotic genes are rare, and that there is little evidence for its use in adult somatic cells; Lewin has been taken out of context and undermines the office's position in that once a gene is transcribed, it is more likely that not that the mRNA will be translated to produce protein; Fu et al. predictability of protein translation is not solely contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation; Mallampalli et al. RT-PCR and Southern analysis are more sensitive than Western blot analysis. Lastly, Applicants have provided a evidence in a form of a Rul 1.132 declaration by Dr. Karen Morrison which provides data showing that the protein of interest is expressed in prostate and lung cancer cells and that the protein can be detected immunohistochemically.

These arguments have been considered, but are not found persuasive.

In response to Applicants arguments pertaining to the utility of the instantly claimed protein as a therapeutic target for the treatment of cancerous prostate cancer cells, the Examiner recognizes and agrees with Applicants assertion that the novel gene, which encodes the target protein, expresses

mRNA in cancerous prostate cancer cells (Specification, page 75, line 13 to page 76, line 8, see also Figures 4 and 5); and further, that the claimed polypeptide is expressed in prostate cancer cells (Morrison Declaration). However, as stated above, if a molecule such as the polypeptide of SEQ ID NO: 2 is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polypeptide to be used in a diagnostic and/or a therapeutic manner. Many polypeptides may be expressed in normal tissues, as well as diseased tissues. For example, as argued by Applicants "[t]he novel gene, which encodes the target protein, expresses mRNA in normal and cancerous prostate cancer cells." (emphasis added) Therefore, if one of ordinary skill in the art would have a reasonable belief that protein would be expressed by the mRNA transcripts detected in the target cells as stated by Applicants, one would expect that the since the mRNA which encodes the protein is found in normal prostate tissues so would the protein. As such, the antibody, which specifically binds the protein, labeled with a radioisotope would deliver and irradiated both cancer cells and normal cells (Applicants Remarks, page 9). Along the same lines, it does not appear that the asserted utility is practical, based upon a well-recognized need in the art for additional prostate cancer markers, because it does not appear that the protein would show selective expression on prostate cancer cells over normal prostate. In response to Applicants arguments pertaining to the publication's cited by the Examiner to support the Office's position that there is not correlation between mRNA expression and protein expression, the Examiner recognizes that the arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). While Applicants have clearly set forth that the claimed protein is expressed in prostate and lung cancers through the Morrison declaration, there is a mountain of evidence, in addition to the references cited above, to indicate that over expression of a particular nucleic acid specific for a tissue type, does not necessarily correlate nor predict equivalent levels of polypeptide expression. Recently, Greenbaum *et al.* (Genome Biology, 2003, Vol. 4, Issue 9, pages 117.1-117.8) cautioned against assuming that mRNA levels are generally correlative of protein levels. The reference teaches (page 117.3, 2nd column) that primarily because of a limited ability to measure protein abundances, researchers have tried to find correlations between mRNA and the limited protein expression data, in the hope that they could determine protein abundance levels from the more copious and technically easier mRNA experiments. To date, however, there have been only a

handful of efforts to find correlations between mRNA and protein expression levels, most notably in human cancers and yeast cells. And, for the most part, they have reported only minimal and/or limited correlations. The reference further teaches (page 117.4, 2nd column) that there are presumably at least three reasons for the poor correlations generally reported in the literature between the level of mRNA and the level of protein, and these may not be mutually exclusive. First, there are many complicated and varied post-transcriptional mechanisms involved in turning mRNA into protein that are not yet sufficiently well defined to be able to compute protein concentrations from mRNA; second, proteins may differ substantially in their *in vivo* half lives; and/or third, there is a significant amount of error and noise in both protein and mRNA experiments that limit our ability to get a clear picture. The reference further notes (page 117.6, page 2nd column) that to be fully able to understand the relationship between mRNA and protein abundances, the dynamic processes involved in protein synthesis and degradation have to be better understood. Lastly, with respect to the Declaration by Dr. Morrison, the Examiner acknowledges the data presented in the declaration and the opinions set forth by Dr. Morrison (page 3). While the Examiner concedes that the declaration shows that the protein is produced in prostate and lung cancer which can be detected via antibodies, the Examiner does not agree with the opinion that the level of expression of 84P2A9 is higher in cancer tissue than in normal tissue because the declaration does not appear to suggest whether the protein is expressed in cancerous tissues to the exclusion of normal. Nor does the declaration nor specification appear to suggest any quantitative measurements. Thus, in the absence of any correlation between the claimed polypeptide with any known disease or disorder, any information obtained from various expression profiles in both normal and diseased tissue only serves as the basis for further research on the observation itself.

New Rejections:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14-15 and 39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. THIS IS A BIOLOGICAL DEPOSIT REJECTION.

Because a microorganism is recited in the claims, it is essential to the invention recited in those claims. It must therefore be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. If the microorganism is not so obtainable or available, the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the microorganism. The specification does not disclose a repeatable process to obtain the microorganism from a source, and it is not apparent if the microorganism is readily available to the public. It is noted that Applicants have deposited the organism under the requirements of the Budapest Treaty on January 6, 2000 with the American Type Culture Collection (ATCC), 1081 University Blvd. Manassas, VA 20110-2209 USA, and have identified it as ATCC Accession No. PTA-1151, but there is no indication in the specification as to public availability.

If the deposit was made under the terms of the Budapest Treaty, as it appears to have been from the enclosed Receipt from the ATCC, then an affidavit or declaration by Applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific strain will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein.

All other previous rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brandon J Fetterolf, PhD
Examiner
Art Unit 1642

BF

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER
1/9/05